Step 2.

Each sample was diluted to 0.24% (by adding 2.5 g more oil) and mixed for 2 hours and heated @ 50° C. for 30 min and mixed again for one hour. All the samples were still cloudy. Samples were kept at room temperature overnight to see if they precipitate or if un-dissolved API settles out. After 20 hours at room temperature, it was observed that all samples still had un-dissolved API.

Step 3.

Each sample was diluted to 0.2% (by adding 2.5 g more oil) and mixed 2 for hours and heated @ 50° C. for 30 min and mixed again for one hour. All the samples were still slightly cloudy, indicating that the estradiol was not completely dissolved.

TABLE 20

Ingredient	Estradiol Solubility (mg/g)	Estradiol Solubility (% w/w)
Peanut Oil	<2	<0.2
Safflower Oil	<2	<0.2
Soy Bean Oil	<2	<0.2

The solubility of estradiol in all three oils was less than 2 mg/g (0.2% w/w). This level of solubility is significantly below the solubility that the present inventors have discovered can be achieved in other oils, e.g., medium chain fatty acid esters, such as the mono/diglycerides, propylene glycol esters, and polyethylene glycol esters discussed above.

In sum, if no heat is used to dissolve estradiol in safflower oil, it will not go into solution. Given that the estradiol did not dissolve at 50 C., oils such as safflower oil will not be useful in the methods of the invention using medium chain fatty acid esters as described hereinabove.

Example 18

Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of Prometrium and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37 C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from Prometrium. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progestrone dissolution from the 200 mg progesterone capsule of the invention and from Prometrium is attached as FIG. **5**.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

We claim:

1. A pharmaceutical formulation for administering estradiol and progesterone to a mammal in need thereof, comprising

solubilized estradiol,

solubilized progesterone,

suspended progesterone, and

an oil,

wherein each of the solubilized estradiol, the solubilized progesterone, and the suspended progesterone is present in the oil, and

wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids.

2. The pharmaceutical formulation of claim **1** wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, and wherein the medium chain fatty acid esters are predominantly esters of

C6 to C10 fatty acids.

3. The pharmaceutical formulation of claim **1** wherein the oil is predominantly mono- and diglycerides.

4. The pharmaceutical formulation of claim **1** wherein at least 90% of the total estradiol is solubilized.

5. The pharmaceutical formulation of claim **1** further comprising a surfactant.

6. The pharmaceutical formulation of claim **5** wherein the surfactant is a non-ionic surfactant.

7. The pharmaceutical formulation of claim **6** wherein the surfactant is lauroyl polyoxyl-32-glycerides.

8. The pharmaceutical formulation of claim **1** comprising:

30 to 35 wt % progesterone,

0.1 to 0.4 wt % estradiol

55 to 75 wt % of the oil, wherein the oil is predominantly medium chain fatty acid mono- and diglycerides, and

0.5 to 10wt % non-ionic surfactant.

9. The pharmaceutical formulation of claim **8** further comprising gelatin, glycerol, and coloring agents.

10. The pharmaceutical formulation of claim **1** wherein the progesterone is released more rapidly than progesterone in peanut oil.

11. The pharmaceutical formulation of claim **1** wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, and wherein the medium chain fatty acid esters are predominantly esters of C8 to C12 fatty acids.